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**Patentanmeldung Nr. Patent application No. Demande de brevet n°**

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**Blatt 2 der Bescheinigung  
Sheet 2 of the certificate  
Page 2 de l'attestation**

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**New pharmaceutical compositions based on anticholinergics and soluble tnfr receptor fusion proteins**

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**NEW PHARMACEUTICAL COMPOSITIONS BASED ON ANTICHOLINERGICS  
AND SOLUBLE TNF RECEPTOR FUSION PROTEINS**

5 The present invention relates to novel pharmaceutical compositions based on anticholinergics and soluble TNF receptor fusion proteins, processes for preparing them and their use in the treatment of respiratory diseases.

**Description of the invention**

10 The present invention relates to novel pharmaceutical compositions based on anticholinergics and soluble TNF receptor fusion proteins, processes for preparing them and their use in the treatment of respiratory diseases.

Surprisingly, an unexpectedly beneficial therapeutic effect, particularly a synergistic effect can be observed in the treatment of inflammatory and/or obstructive diseases of the respiratory tract if one or more, preferably one, anticholinergic is used with one or more, preferably one, soluble TNF receptor fusion protein. In view of this synergistic effect the pharmaceutical combinations according to the invention can be used in smaller doses than would be the case with the individual compounds used in monotherapy in the usual way. The effects mentioned above may be observed both when the two active substances are administered simultaneously in a single active substance formulation and when they are administered successively in separate formulations. According to the invention, it is preferable to administer the two active substance ingredients simultaneously in a single formulation.

25 Within the scope of the present invention the term anticholinergics 1 denotes salts which are preferably selected from among tiotropium salts, oxitropium salts and ipratropium salts, most preferably tiotropium salts. In the above-mentioned salts the cations tiotropium, oxitropium and ipratropium are the pharmacologically active ingredients. Within the scope of the present patent application, any reference to the above cations is indicated by the use of the number 1. Any reference to compounds 1 naturally also includes a reference to the ingredients 1 (tiotropium, oxitropium or ipratropium).

30 By the salts 1 which may be used within the scope of the present invention are meant the compounds which contain, in addition to tiotropium, oxitropium or ipratropium as counter-ion (anion), chloride, bromide, iodide, methanesulphonate or para-toluenesulphonate. Within the scope of the present invention, the methanesulphonate, chloride, bromide and iodide are preferred of all the salts 1, the methanesulphonate and

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bromide being of particular importance. Of outstanding importance according to the invention are salts 1 selected from among tiotropium bromide, oxitropium bromide and ipratropium bromide. Tiotropium bromide is particularly preferred. Within the scope of the present invention the term anticholinergics 1 denotes the aforementioned salts optionally in form of their hydrates or solvates. In case of the preferred anticholinergic 1, tiotropium bromide, the crystalline monohydrate as described in WO 02/30928 is of particular interest.

Within the scope of the present invention, the term soluble TNF receptor fusion proteins (hereinafter 2) denotes compounds, which contain at least one TNF alpha binding site derived from a TNF alpha receptor (fused with other protein fragments such as the Fc portion of an immunoglobulin molecule) and which can be modified by pegylation. Of outstanding importance according to the invention are lenercept and etanercept. A particular preferred soluble TNF receptor fusion protein 2 is etanercept.

The pharmaceutical combinations of 1 and 2 according to the invention are preferably administered by inhalation. Suitable inhalable powders packed into suitable capsules (inhalettes) may be administered using suitable powder inhalers. The drug may also be inhaled using suitable solutions of the pharmaceutical combination consisting of 1 and 2.

In one aspect, therefore, the invention relates to a pharmaceutical composition which contains a combination of 1 and 2. In another aspect the present invention relates to a pharmaceutical composition which contains one or more salts 1 and one or more compounds 2, optionally in the form of their solvates or hydrates. Again, the active substances may be combined in a single preparation or contained in two separate formulations. Pharmaceutical compositions which contain the active substances 1 and 2 in a single preparation are preferred according to the invention.

In another aspect the present invention relates to a pharmaceutical composition which contains, in addition to therapeutically effective quantities of 1 and 2, a pharmaceutically acceptable excipient. In another aspect the present invention relates to a pharmaceutical composition which does not contain any pharmaceutically acceptable excipient in addition to therapeutically effective quantities of 1 and 2.

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The present invention also relates to the use of 1 and 2 for preparing a pharmaceutical composition containing therapeutically effective quantities of 1 and 2 for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD). Other diseases where the combination is useful are inflammatory diseases of the lung associated with fibrosis, such as cystic fibrosis and inflammatory diseases of the upper airways such as rhinitis.

The present invention also relates to the use of 1 for preparing a pharmaceutical composition for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD), characterized in that a therapeutically effective quantity of 2 is used as well.

The present invention also relates to the simultaneous or successive use of therapeutically effective doses of the combination of the above pharmaceutical compositions 1 and 2 for treating inflammatory and/or obstructive diseases of the respiratory tract, particularly asthma or chronic obstructive pulmonary disease (COPD) as well as allergic and non-allergic rhinitis, and cystic fibrosis, by simultaneous or successive administration.

In the active substance combinations of 1 and 2, ingredient 1 may be present in the form of enantiomers, mixtures of enantiomers or in the form of racemates, whilst ingredient 2 may be present as a glycosylated protein whereby the degree and type of glycosylation may be varied.

The proportions in which the two active substances 1 and 2 may be used in the active substance combinations according to the invention are variable. Active substances 1 and 2 may possibly be present in the form of their solvates or hydrates. Depending on the choice of the compounds 1 and 2, the weight ratios which may be used within the scope of the present invention vary on the basis of the different molecular weights of the various compounds and their different potencies.

As a rule, the pharmaceutical combinations according to the invention may contain compounds 1 and 2 in ratios by weight ranging from 1:2000 to 1:1, preferably from 1:1000 to 1:5. In the particularly preferred pharmaceutical combinations which contain tiotropium salt as compound 1, the weight ratios of 1 to 2 are most preferably in a range in which ipratropium or tiotropium 1' and 2 are present in proportions of 1:500 to 1:10, more

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preferably from 1:200 to 1:20. For example, without restricting the scope of the invention thereto, preferred combinations of 1 and 2 according to the invention may contain tiotropium 1' and anti TNF antibody 2 in the following weight ratios: 1:200 1:100; 1:90; 1:85; 1:80; 1:75; 1:70; 1:65; 1:60; 1:55; 1:50; 1:49; 1:48; 1:47; 1:46; 1:45; 1:44; 1:43; 1:42; 1:41; 1:40; 1:39; 1:38; 1:37; 1:36; 1:35; 1:34; 1:33; 1:32; 1:31; 1:30; 1:29; 1:28; 1:27; 1:26; 1:25; 1:24; 1:23; 1:22; 1:21; 1:20

The pharmaceutical compositions according to the invention containing the combinations of 1 and 2 are normally administered so that 1 and 2 are present together in doses of 1 to 10000µg, preferably from 10 to 5000µg, more preferably from 100 to 5000µg, better still from 1000 to 2000µg per single dose. For example, combinations of 1 and 2 according to the invention contain a quantity of tiotropium 1' and 2 such that the total dosage per single dose is about 100µg, 105µg, 110µg, 115µg, 120µg, 125µg, 130µg, 135µg, 140µg, 145µg, 150µg, 155µg, 160µg, 165µg, 170µg, 175µg, 180µg, 185µg, 190µg, 195µg, 200µg, 205µg, 210µg, 215µg, 220µg, 225µg, 230µg, 235µg, 240µg, 245µg, 250µg, 255µg, 260µg, 265µg, 270µg, 275µg, 280µg, 285µg, 290µg, 295µg, 300µg, 305µg, 310µg, 315µg, 320µg, 325µg, 330µg, 335µg, 340µg, 345µg, 350µg, 355µg, 360µg, 365µg, 370µg, 375µg, 380µg, 385µg, 390µg, 395µg, 400µg, 405µg, 410µg, 415µg, 420µg, 425µg, 430µg, 435µg, 440µg, 445µg, 450µg, 455µg, 460µg, 465µg, 470µg, 475µg, 480µg, 485µg, 490µg, 495µg, 500µg, 505µg, 510µg, 515µg, 520µg, 525µg, 530µg, 535µg, 540µg, 545µg, 550µg, 555µg, 560µg, 565µg, 570µg, 575µg, 580µg, 585µg, 590µg, 595µg, 600µg, 605µg, 610µg, 615µg, 620µg, 625µg, 630µg, 635µg, 640µg, 645µg, 650µg, 655µg, 660µg, 665µg, 670µg, 675µg, 680µg, 685µg, 690µg, 695µg, 700µg, 705µg, 710µg, 715µg, 720µg, 725µg, 730µg, 735µg, 740µg, 745µg, 750µg, 755µg, 760µg, 765µg, 770µg, 775µg, 780µg, 785µg, 790µg, 795µg, 800µg, 805µg, 810µg, 815µg, 820µg, 825µg, 830µg, 835µg, 840µg, 845µg, 850µg, 855µg, 860µg, 865µg, 870µg, 875µg, 880µg, 885µg, 890µg, 895µg, 900µg, 905µg, 910µg, 915µg, 920µg, 925µg, 930µg, 935µg, 940µg, 945µg, 950µg, 955µg, 960µg, 965µg, 970µg, 975µg, 980µg, 985µg, 990µg, 995µg, 1000µg, 1005µg, 1010µg, 1015µg, 1020µg, 1025µg, 1030µg, 1035µg, 1040µg, 1045µg, 1050µg, 1055µg, 1060µg, 1065µg, 1070µg, 1075µg, 1080µg, 1085µg, 1090µg, 1095µg, 1100µg, 1105µg, 1110µg, 1115µg, 1120µg, 1125µg, 1130µg, 1135µg, 1140µg, 1145µg, 1150µg, 1155µg, 1160µg, 1165µg, 1170µg, 1175µg, 1180µg, 1185µg, 1190µg, 1195µg, 1200µg, 1250µg, 1300µg, 1350µg, 1400µg, 1450µg, 1500µg, 1550µg, 1600µg, 1650µg, 1700µg, 1750µg, 1800µg, 1850µg, 1900µg, 1950µg, 2000µg or similar. The suggested dosages per single dose specified above are not to be

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regarded as being limited to the numerical values actually stated, but are intended as dosages which are disclosed by way of example. Of course, dosages which may fluctuate about the abovementioned numerical values within a range of about  $\pm 2.5 \mu\text{g}$  are also included in the values given above by way of example. In these dosage ranges, the active substances 1' and 2 may be present in the weight ratios given above.

For example, without restricting the scope of the invention thereto, the combinations of 1 and 2 according to the invention may contain a quantity of tiotropium 1' and soluble TNF receptor fusion protein 2 such that, for each single dose,  $5 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $5 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $10 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $18 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $20 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $36 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $50 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $100 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $200 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $300 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $400 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $500 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $600 \mu\text{g}$  of 2 or  $40 \mu\text{g}$  of 1' and  $700 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $800 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $900 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $1000 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $1500 \mu\text{g}$  of 2,  $40 \mu\text{g}$  of 1' and  $2000 \mu\text{g}$  of 2 are administered

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If the active substance combination in which 1 denotes tiotropium bromide is used as the preferred combination of 1 and 2 according to the invention, the quantities of active substance 1 and 2 administered per single dose mentioned by way of example correspond to the following quantities of 1 and 2 administered per single dose: 6µg of 1 and 50µg of 2, 6µg of 1 and 100µg of 2, 6µg of 1 and 200µg of 2, 6µg of 1 and 300µg of 2, 6µg of 1 and 400µg of 2, 6µg of 1 and 500µg of 2, 6µg of 1 and 600µg of 2, 6µg of 1 and 700µg of 2, 6µg of 1 and 800µg of 2, 6µg of 1 and 900µg of 2, 6µg of 1 and 1000µg of 2, 6µg of 1 and 1500µg of 2, 6µg of 1 and 2000µg of 2, 12µg of 1 and 50µg of 2, 12µg of 1 and 100µg of 2, 12µg of 1 and 200µg of 2, 12µg of 1 and 300µg of 2, 12µg of 1 and 400µg of 2, 12µg of 1 and 500µg of 2, 12µg of 1 and 600µg of 2, 12µg of 1 and 700µg of 2, 12µg of 1 and 800µg of 2, 12µg of 1 and 900µg of 2, 12µg of 1 and 1000µg of 2, 12µg of 1 and 1500µg of 2, 12µg of 1 and 2000µg of 2, 21.7µg of 1 and 50µg of 2, 21.7µg of 1 and 100µg of 2, 21.7µg of 1 and 200µg of 2, 21.7µg of 1 and 300µg of 2, 21.7µg of 1 and 400µg of 2, 21.7µg of 1 and 500µg of 2, 21.7µg of 1 and 600µg of 2, 21.7µg of 1 and 700µg of 2, 21.7µg of 1 and 800µg of 2, 21.7µg of 1 and 900µg of 2, 21.7µg of 1 and 1000µg of 2, 21.7µg of 1 and 1500µg of 2, 21.7µg of 1 and 2000µg of 2, 24.1µg of 1 and 50µg of 2, 24.1µg of 1 and 100µg of 2, 24.1µg of 1 and 200µg of 2, 24.1µg of 1 and 300µg of 2, 24.1µg of 1 and 400µg of 2, 24.1µg of 1 and 500µg of 2, 24.1µg of 1 and 600µg of 2, 24.1µg of 1 and 700µg of 2, 24.1µg of 1 and 800µg of 2, 24.1µg of 1 and 900µg of 2, 24.1µg of 1 and 1000µg of 2, 24.1µg of 1 and 1500µg of 2, 24.1µg of 1 and 2000µg of 2, 43.3µg of 1 and 50µg of 2, 43.3µg of 1 and 100µg of 2, 43.3µg of 1 and 200µg of 2, 43.3µg of 1 and 300µg of 2, 43.3µg of 1 and 400µg of 2, 43.3µg of 1 and 500µg of 2, 43.3µg of 1 and 600µg of 2, 43.3µg of 1 and 700µg of 2, 43.3µg of 1 and 800µg of 2, 43.3µg of 1 and 900µg of 2, 43.3µg of 1 and 1000µg of 2, 43.3µg of 1 and 1500µg of 2, 43.3µg of 1 and 2000µg of 2, 48.1µg of 1 and 50µg of 2, 48.1µg of 1 and 100µg of 2, 48.1µg of 1 and 200µg of 2, 48.1µg of 1 and 300µg of 2, 48.1µg of 1 and 400µg of 2, 48.1µg of 1 and 500µg of 2, 48.1µg of 1 and 600µg of 2, 48.1µg of 1 and 700µg of 2, 48.1µg of 1 and 800µg of 2, 48.1µg of 1 and 900µg of 2, 48.1µg of 1 and 1000µg of 2, 48.1µg of 1 and 1500µg of 2, 48.1µg of 1 and 2000µg of 2.

If the active substance combination in which 1 is tiotropium bromide monohydrate is used as the preferred combination of 1 and 2 according to the invention, the quantities of 1 and 2 administered per single dose specified by way of example hereinbefore correspond to the following quantities of 1 and 2 administered per single dose: 6.2µg of 1 and 50µg of 2, 6.2µg of 1 and 100µg of 2, 6.2µg of 1 and 200µg of 2, 6.2µg of 1 and 300µg of 2, 6.2µg of



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1 and 400µg of 2, 6.2µg of 1 and 500µg of 2, 6.2µg of 1 and 600µg of 2, 6.2µg of 1 and  
 700µg of 2, 6.2µg of 1 and 800µg of 2, 6.2µg of 1 and 900µg of 2, 6.2µg of 1 and 1000µg  
 of 2, 6.2µg of 1 and 1500µg of 2, 6.2µg of 1 and 2000µg of 2, 12.5µg of 1 and 50µg of 2,  
 12.5µg of 1 and 100µg of 2, 12.5µg of 1 and 200µg of 2, 12.5µg of 1 and 300µg of 2,  
 12.5µg of 1 and 400µg of 2, 12.5µg of 1 and 500µg of 2, 12.5µg of 1 and 600µg of 2,  
 12.5µg of 1 and 700µg of 2, 12.5µg of 1 and 800µg of 2, 12.5µg of 1 and 900µg of 2,  
 12.5µg of 1 and 1000µg of 2, 12.5µg of 1 and 1500µg of 2, 12.5µg of 1 and 2000µg of 2,  
 22.5µg of 1 and 50µg of 2, 22.5µg of 1 and 100µg of 2, 22.5µg of 1 and 200µg of 2,  
 22.5µg of 1 and 300µg of 2, 22.5µg of 1 and 400µg of 2, 22.5µg of 1 and 500µg of 2,  
 22.5µg of 1 and 600µg of 2, 22.5µg of 1 and 700µg of 2, 22.5µg of 1 and 800µg of 2,  
 22.5µg of 1 and 900µg of 2, 22.5µg of 1 and 1000µg of 2, 22.5µg of 1 and 1500µg of 2,  
 22.5µg of 1 and 2000µg of 2, 25µg of 1 and 50µg of 2, 25µg of 1 and 100µg of 2, 25µg of  
 1 and 200µg of 2, 25µg of 1 and 300µg of 2, 25µg of 1 and 400µg of 2, 25µg of 1 and  
 500µg of 2, 25µg of 1 and 600µg of 2, 25µg of 1 and 700µg of 2, 25µg of 1 and 800µg of  
 2, 25µg of 1 and 900µg of 2, 25µg of 1 and 1000µg of 2, 25µg of 1 and 1500µg of 2, 25µg  
 of 1 and 2000µg of 2, 45µg of 1 and 50µg of 2, 45µg of 1 and 100µg of 2, 45µg of 1 and  
 200µg of 2, 45µg of 1 and 300µg of 2, 45µg of 1 and 400µg of 2, 45µg of 1 and 500µg of  
 2, 45µg of 1 and 600µg of 2, 45µg of 1 and 700µg of 2, 45µg of 1 and 800µg of 2, 45µg of  
 1 and 900µg of 2, 45µg of 1 and 1000µg of 2, 45µg of 1 and 1500µg of 2, 45µg of 1 and  
 2000µg of 2, 50µg of 1 and 50µg of 2, 50µg of 1 and 100µg of 2, 50µg of 1 and 200µg of  
 2, 50µg of 1 and 300µg of 2, 50µg of 1 and 400µg of 2, 50µg of 1 and 500µg of 2, 50µg of  
 1 and 600µg of 2, 50µg of 1 and 700µg of 2, 50µg of 1 and 800µg of 2, 50µg of 1 and  
 900µg of 2 or 50µg of 1 and 1000µg of 2, 50µg of 1 and 1500µg of 2, 50µg of 1 and  
 2000µg of 2

The active substance combinations of 1 and 2 according to the invention are preferably  
 administered by inhalation. For this purpose, ingredients 1 and 2 have to be made available  
 in forms suitable for inhalation. Inhalable preparations include inhalable powders and  
 inhalable solutions. Inhalable powders according to the invention containing the  
 combination of active substances 1 and 2 may consist of the active substances on their own  
 or of a mixture of the active substances with physiologically acceptable excipients. Within  
 the scope of the present invention, inhalable solutions also includes concentrates or sterile  
 inhalable solutions ready for use in a nebuliser. The preparations according to the invention  
 may contain the combination of active substances 1 and 2 either together in one  
 formulation or in two separate formulations. These formulations which may be used within

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the scope of the present invention are described in more detail in the next part of the specification.

A) Inhalable powder containing the combinations of active substances 1 and 2 according to the invention:

The inhalable powders according to the invention may contain 1 and 2 either on their own or in admixture with suitable physiologically acceptable excipients.

If the active substances 1 and 2 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g. glucose or arabinose), disaccharides (e.g. lactose, saccharose, maltose, trehalose), oligo- and polysaccharides (e.g. dextran), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another.

Preferably, mono- or disaccharides are used, while the use of lactose, trehalose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

Within the scope of the inhalable powders according to the invention the excipients have a maximum mass mean aerodynamic diameter of up to  $250\mu\text{m}$ , preferably between 10 and  $150\mu\text{m}$ , most preferably between 15 and  $80\mu\text{m}$ . It may sometimes seem appropriate to add finer excipient fractions with an mass mean aerodynamic diameter of 1 to  $9\mu\text{m}$  to the excipient mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore.

Finally, in order to prepare the inhalable powders according to the invention, active substance 1 and 2, preferably with an mass mean aerodynamic diameter of 0.5 to  $10\mu\text{m}$ , more preferably from 1 to  $5\mu\text{m}$ , is added to the excipient mixture. Processes for producing the inhalable powders according to the invention and finally mixing the ingredients together are known from the prior art. These processes may include, but are not limited to, spray drying or grinding and micronising. Particularly favoured are processes which protect the protein component from denaturation during the production of particles of the right size range to be suitable for inhalation. The inhalable powders according to the invention may be prepared and administered either in the form of a single powder mixture

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which contains both 1 and 2 or in the form of separate inhalable powders which contain only 1 or 2.

The inhalable powders according to the invention may be administered using inhalers known from the prior art. Inhalable powders according to the invention which contain a physiologically acceptable excipient in addition to 1 and 2 may be administered, for example, by means of inhalers which deliver a single dose from a supply using a measuring chamber as described in US 4570630A, or by other means as described in DE 36 25 685 A. Preferably, the inhalable powders according to the invention which contain physiologically acceptable excipient in addition to 1 and 2 are packed into capsules (to produce so-called inhalettes) which are used in inhalers as described, for example, in WO 94/28958.

A particularly preferred inhaler for using the pharmaceutical combination according to the invention in inhalettes is shown in Figure 1.

This inhaler (Handihaler) for inhaling powdered pharmaceutical compositions from capsules is characterised by a housing 1 containing two windows 2, a deck 3 in which there are air inlet ports and which is provided with a screen 5 secured via a screen housing 4, an inhalation chamber 6 connected to the deck 3 on which there is a push button 9 provided with two sharpened pins 7 and movable counter to a spring 8, a mouthpiece 12 which is connected to the housing 1, the deck 3 and a cover 11 via a spindle 10 to enable it to be flipped open or shut and three holes 13 with diameters below 1 mm in the central region around the capsule chamber 6 and underneath the screen housing 4 and screen 5.

The main air flow enters the inhaler between deck 3 and base 1 near to the hinge. The deck has in this range a reduced width, which forms the entrance slit for the air. Then the flow reverses and enters the capsule chamber 6 through the inlet tube. The flow is then further conducted through the filter and filter holder to the mouthpiece. A small portion of the flow enters the device between mouthpiece and deck and flows then between filterholder and deck into the main stream. Due to production tolerances there is some uncertainty in this flow because of the actual width of the slit between filterholder and deck. In case of new or reworked tools the flow resistance of the inhaler may therefore be a little off the target value. To correct this deviation the deck has in the central region around the capsule chamber 6 and underneath the screen housing 4 and screen 5 three holes 13 with diameters below 1 mm. Through these holes 13 flows air from the base into the main air stream and reduces such slightly the flow resistance of the inhaler. The actual diameter of these holes

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13 can be chosen by proper inserts in the tools so that the mean flow resistance can be made equal to the target value.

5 If the inhalable powders according to the invention are packed into capsules (inhalers) for the preferred use described above, the quantities packed into each capsule should be 1 to 30mg, preferably 3 to 20mg, more particularly 5 to 10mg of inhalable powder per capsule. These capsules contain, according to the invention, either together or separately, the doses of 1 and 2 mentioned hereinbefore for each single dose.

10 B) Inhalable solutions or suspensions containing the combinations of active substances 1 and 2 according to the invention:

In another preferred embodiment the active substance combination according to the invention is used in the form of inhalable solutions and suspensions. The solvent /  
15 suspending agent used may be aqueous or alcoholic, preferably an ethanolic.. The solvent / suspending agent may be water on its own or a mixture of water and ethanol. The relative proportion of ethanol compared with water is not limited (other, than by the requirement that it not cause irreversible denaturation of the protein component of the mixture), but the maximum is up to 70 percent by volume, more particularly up to 60 percent by volume and most preferably up to 30 percent by volume. The remainder of the volume is made up of  
20 water. The solutions or suspensions containing 1 and 2, separately or together, are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid,  
25 malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulphuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may be used, particularly in the case  
30 of acids which have other properties in addition to their acidifying qualities, e.g. as flavourings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

35 According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser or complexing agent is unnecessary in the present

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formulation. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium edetate is less than 100mg/100ml, preferably less than 50mg/100 ml, more preferably less than 20mg/100 ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10mg/100ml are preferred.

Co-solvents and/or other excipients may be added to the inhalable solutions according to the invention. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g. alcohols - particularly isopropyl alcohol, glycols - particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the pharmacologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins and provitamins occurring in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50mg/100ml, more preferably between 5 and 20mg/100ml.

Preferred formulations contain, in addition to the solvent water and the combination of active substances 1 and 2, only benzalkonium chloride and sodium edetate. In another preferred embodiment, no sodium edetate is present.

5 The inhalable solutions according to the invention are administered in particular using inhalers of the kind which are capable of nebulising a small amount of a liquid formulation in the therapeutic dose within a few seconds to produce an aerosol suitable for therapeutic inhalation. Within the scope of the present invention, preferred inhalers are those in which a quantity of less than 100  $\mu$ L, preferably less than 50  $\mu$ L, more preferably between 10 and 10 30  $\mu$ L of active substance solution can be nebulised in preferably one spray action to form an aerosol with an mass mean aerodynamic diameter of less than 20  $\mu$ m, preferably less than 10  $\mu$ m, in such a way that the inhalable part of the aerosol corresponds to the therapeutically effective quantity.

15 An apparatus of this kind for delivery of a metered quantity of a liquid pharmaceutical composition for inhalation is described for example in International Patent Application WO 91/14468 and also in WO 97/12687 (cf. in particular Figures 6a and 6b). The nebulisers (devices) described therein are known by the name Respimat®. This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols 20 according to the invention containing the combination of active substances 1 and 2. Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, this device can be carried at all times by the patient. The nebuliser sprays a defined volume of pharmaceutical formulation using high pressures through small nozzles so as to produce inhalable aerosols.

25 The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking mechanism, a spring housing, a spring and a storage container, characterised by

- 30 - a pump housing which is secured in the upper housing part and which comprises at one end a nozzle body with the nozzle or nozzle arrangement,
- a hollow plunger with valve body,
- a power takeoff flange in which the hollow plunger is secured and which is located in the upper housing part,
- a locking mechanism situated in the upper housing part,

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- a spring housing with the spring contained therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
- a lower housing part which is fitted onto the spring housing in the axial direction.

5 The hollow plunger with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is axially movable within the cylinder. Reference is made in particular to Figures 1 to 4, especially Figure 3, and the relevant parts of the description. The hollow plunger with valve body exerts a pressure of 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the  
10 fluid, the measured amount of active substance solution, at its high pressure end at the moment when the spring is actuated. Volumes of 10 to 50 microlitres are preferred, while volumes of 10 to 20 microlitres are particularly preferred and a volume of 15 microlitres per spray is most particularly preferred.

15 The valve body is preferably mounted at the end of the hollow plunger facing the valve body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by microtechnology. Microstructured nozzle bodies are disclosed for example in  
20 WO-94/07607; reference is hereby made to the contents of this specification, particularly Figure 1 therein and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon firmly joined together, at least one of which has one or more microstructured channels which connect the  
25 nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns while the length is preferably 7 to 9 microns.

In the case of a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may extend parallel to one another or may be inclined  
30 relative to one another in the direction of the nozzle opening. In a nozzle body with at least two nozzle openings at the outlet end the directions of spraying may be at an angle of 20 to 160° to one another, preferably 60 to 150°, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, most preferably 30 to 70 microns. Spacings of 50 microns

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are most preferred. The directions of spraying will therefore meet in the vicinity of the nozzle openings.

5 The liquid pharmaceutical preparation strikes the nozzle body with an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised into an inhalable aerosol through the nozzle openings. The preferred particle or droplet sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

10 The locking mechanism contains a spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power takeoff flange as an actuating member the movement of which is determined by the position of a locking member. The travel of the power takeoff flange is precisely limited by an upper and lower stop. The spring is preferably biased, via a power step-up gear, e.g. a helical thrust gear, by an external torque which is produced when the upper housing part is rotated counter to the  
15 spring housing in the lower housing part. In this case, the upper housing part and the power takeoff flange have a single or multiple V-shaped gear.

20 The locking member with engaging locking surfaces is arranged in a ring around the power takeoff flange. It consists, for example, of a ring of plastic or metal which is inherently radially elastically deformable. The ring is arranged in a plane at right angles to the atomiser axis. After the biasing of the spring, the locking surfaces of the locking member move into the path of the power takeoff flange and prevent the spring from relaxing. The locking member is actuated by means of a button. The actuating button is connected or  
25 coupled to the locking member. In order to actuate the locking mechanism, the actuating button is moved parallel to the annular plane, preferably into the atomiser; this causes the deformable ring to deform in the annular plane. Details of the construction of the locking mechanism are given in WO 97/20590.

30 The lower housing part is pushed axially over the spring housing and covers the mounting, the drive of the spindle and the storage container for the fluid.

35 When the atomiser is actuated the upper housing part is rotated relative to the lower housing part, the lower housing part taking the spring housing with it. The spring is thereby compressed and biased by means of the helical thrust gear and the locking mechanism engages automatically. The angle of rotation is preferably a whole-number



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fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is biased, the power takeoff part in the upper housing part is moved along by a given distance, the hollow plunger is withdrawn inside the cylinder in the pump housing, as a result of which some of the fluid is sucked out of the storage container and into the high pressure chamber in front of the nozzle.

If desired, a number of exchangeable storage containers which contain the fluid to be atomised may be pushed into the atomiser one after another and used in succession. The storage container contains the aqueous aerosol preparation according to the invention.

The atomising process is initiated by pressing gently on the actuating button. As a result, the locking mechanism opens up the path for the power takeoff member. The biased spring pushes the plunger into the cylinder of the pump housing. The fluid leaves the nozzle of the atomiser in atomised form.

Further details of construction are disclosed in PCT Applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

The components of the atomiser (nebuliser) are made of a material which is suitable for its purpose. The housing of the atomiser and, if its operation permits, other parts as well are preferably made of plastics, e.g. by injection moulding. For medicinal purposes, physiologically safe materials are used.

Figures 6a/b of WO 97/12687, show the nebuliser (Respimat®) which can advantageously be used for inhaling the aqueous aerosol preparations according to the invention.

Figure 6a of WO 97/12687 shows a longitudinal section through the atomiser with the spring biased while Figure 6b shows a longitudinal section through the atomiser with the spring relaxed.

The upper housing part (51) contains the pump housing (52) on the end of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow plunger (57) fixed in the power takeoff flange (56) of the locking mechanism projects partially into the cylinder of the pump housing. At its end the hollow plunger carries the valve body (58). The hollow plunger is sealed off by means of the seal (59). Inside the upper housing part is the stop (60) on which the power takeoff flange abuts when the spring is relaxed. On the power takeoff flange is the stop (61) on which the power takeoff flange abuts when the spring is biased. After the biasing of the spring the

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locking member (62) moves between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The upper housing part ends in the mouthpiece (65) and is sealed off by means of the protective cover (66) which can be placed thereon.

5 The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-in lugs (69) and rotary bearing. The lower housing part (70) is pushed over the spring housing. Inside the spring housing is the exchangeable storage container (71) for the fluid (72) which is to be atomised. The storage container is sealed off by the stopper (73) through which the hollow plunger projects into the storage  
10 container and is immersed at its end in the fluid (supply of active substance solution). The spindle (74) for the mechanical counter is mounted in the covering of the spring housing. At the end of the spindle facing the upper housing part is the drive pinion (75). The slider (76) sits on the spindle.

15 The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to produce an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the method described above (Respimat®) the quantity delivered should correspond to a defined quantity with a  
20 tolerance of not more than 25%, preferably 20% of this amount in at least 97%, preferably at least 98% of all operations of the inhaler (spray actuations). Preferably, between 5 and 30 mg of formulation, most preferably between 5 and 20 mg of formulation are delivered as a defined mass on each actuation.

25 However, the formulation according to the invention may also be nebulised by means of inhalers other than those described above, e.g. jet stream inhalers.

Accordingly, in a further aspect, the invention relates to pharmaceutical formulations in the form of inhalable solutions or suspensions as described above combined with a device  
30 suitable for administering these formulations, preferably in conjunction with the Respimat®. Preferably, the invention relates to inhalable solutions or suspensions characterised by the combination of active substances 1 and 2 according to the invention in conjunction with the device known by the name Respimat®. In addition, the present invention relates to the above-mentioned devices for inhalation, preferably the Respimat®.

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characterised in that they contain the inhalable solutions or suspensions according to the invention as described hereinbefore.

The inhalable solutions or suspensions according to the invention may take the form of concentrates or sterile inhalable solutions or suspensions ready for use, as well as the above-mentioned solutions and suspensions designed for use in a Respimat®.

Formulations ready for use may be produced from the concentrates, for example, by the addition of isotonic saline solutions. Sterile formulations ready for use may be administered using energy-operated fixed or portable nebulisers which produce inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other principles.

Accordingly, in another aspect, the present invention relates to pharmaceutical compositions in the form of inhalable solutions or suspensions as described hereinbefore which take the form of concentrates or sterile formulations ready for use, combined with a device suitable for administering these solutions, characterised in that the device is an energy-operated free-standing or portable nebuliser which produces inhalable aerosols by means of ultrasound or compressed air by the Venturi principle or other methods.

The Examples which follow serve to illustrate the present invention in more detail without restricting the scope of the invention to the following embodiments by way of example.

#### Examples of Formulations

##### A) Inhalable powders:

1)

Ingredients	µg per capsule
tiotropium bromide	21.7
etanercept	200
lactose	4778.3
total	5000

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2)

Ingredients	$\mu\text{g}$ per capsule
tiotropium bromide	21.7
etanercept	125
lactose	4853.3
total	5000

3)

Ingredients	$\mu\text{g}$ per capsule
tiotropium bromide x H <sub>2</sub> O	22.5
etanercept	250
lactose	4727.5
total	5000

5 4)

Ingredients	$\mu\text{g}$ per capsule
tiotropium bromide	21.7
etanercept	250
trehalose	4728.3
total	5000

5)

Ingredients	$\mu\text{g}$ per capsule
tiotropium bromide x H <sub>2</sub> O	22.5
etanercept	495
trehalose	4482.5
total	5000

6)

Ingredients	$\mu\text{g}$ per capsule
tiotropium bromide	21.7
etanercept	400
lactose	4578.3
total	5000

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## Patent Claims

- 1) Pharmaceutical composition, characterised in that it contains one or more anticholinergics (1) in combination with one or more soluble TNF receptor fusion proteins (2) optionally in the form of the individual optical isomers, mixtures thereof or racemates and optionally in the form of the pharmacologically acceptable acid addition salts thereof, optionally in the form of the solvates or hydrates and optionally together with a pharmaceutically acceptable excipient.
- 2) Pharmaceutical composition according to claim 1, characterised in that 1 is selected from among the tiotropium salts, oxitropium salts or ipratropium salts, preferably tiotropium salts.
- 3) Pharmaceutical composition according to claim 2, characterised in that 1 is present in the form of the chloride, bromide, iodide, methanesulphonate or para-toluenesulphonate, preferably in the form of the bromide.
- 4) Pharmaceutical composition according to claims 1, 2 or 3, characterised in that 2 is etanercept or lenercept.
- 5) Pharmaceutical composition according to claim 4, characterised in that 2 is etanercept.
- 6) Pharmaceutical composition according to one of claims 1 to 5, characterised in that the active substances 1 and 2 are present either together in a single formulation or in two separate formulations.
- 7) Pharmaceutical composition according to one of claims 1 to 6, characterised in that the weight ratios of 1 to 2 are in the range from 1:2000 to 1:1, preferably from 1:1000 to 1:5.
- 8) Pharmaceutical composition according to one of claims 1 to 7, characterised in that a single administration corresponds to a dose of the active substance combination 1 and 2 of 1 to 10000µg, preferably from 10 to 5000µg.

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- 9) Pharmaceutical composition according to one of claims 1 to 8, characterised in that it is in the form of a formulation suitable for inhalation.
- 10) Pharmaceutical composition according to claim 9, characterised in that it is a formulation selected from among inhalable powders and inhalable solutions or suspensions.
- 11) Pharmaceutical composition according to claim 10, characterised in that it is an inhalable powder which contains 1 and 2 in admixture with suitable physiologically acceptable excipients selected from among the monosaccharides, disaccharides, oligo- and polysaccharides, polyalcohols, salts, or mixtures of these excipients with one another.
- 12) Inhalable powder according to claim 11, characterised in that the excipient has a maximum mass mean aerodynamic diameter of up to 250µm, preferably between 10 and 150µm.
- 13) Capsules, characterised in that they contain an inhalable powder according to claim 11 or 12.
- 14) Pharmaceutical composition according to claim 10, characterised in that it is an inhalable powder which contains only the active substances 1 and 2 as its ingredients.
- 15) Pharmaceutical composition according to claim 10, characterised in that it is an inhalable solution or suspension which contains water, ethanol or a mixture of water and ethanol as solvent.
- 16) Inhalable solution or suspension according to claim 15, characterised in that the pH is 2-7, preferably 2-5.
- 17) Use of a capsule according to claim 13 in an inhaler, preferably in a Handihaler.
- 18) Use of an inhalable solution according to one of claims 15 or 16 for nebulising in an inhaler according to WO 91/14468 or an inhaler as described in Figures 6a and 6b of WO 97/12687.

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19) Use of a composition according to one of claims 1 to 16 for preparing a medicament for treating inflammatory or obstructive diseases of the respiratory tract.

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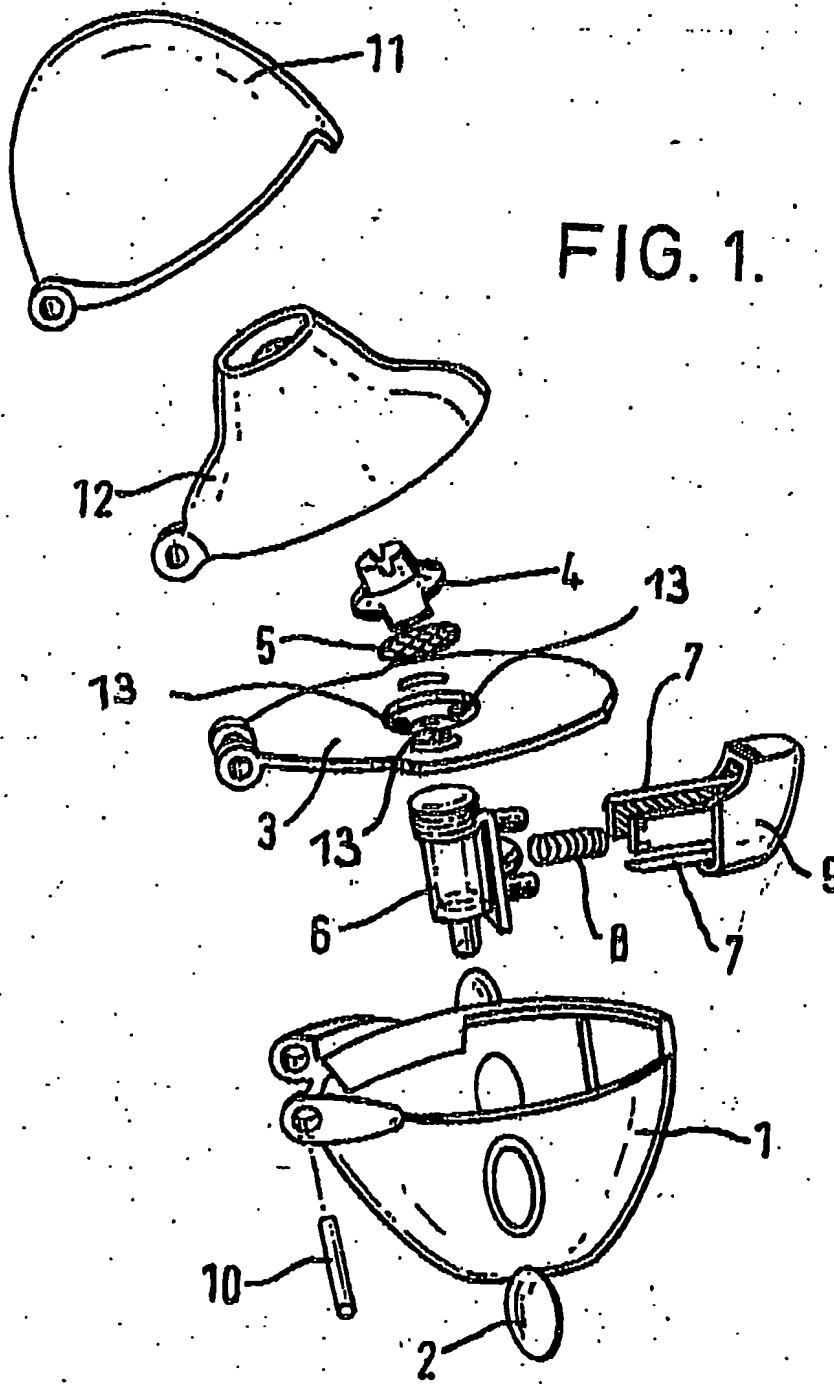
### Abstract

The present invention relates to novel pharmaceutical compositions based on anticholinergics and soluble TNF receptor fusion proteins, processes for preparing them  
5 and their use in the treatment of respiratory diseases.



1/1

FIG. 1.



PCT Application  
**PCT/EP2004/001143**

